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Montréal, Canada

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Andrew Vaillant et al.
ASSIGNEE:	REPLICOR INC.
SERIAL NUMBER:	10/661,403
TITLE:	ANTIVIRAL OLIGONUCLEOTIDES
FILING DATE:	September 12, 2003
ART UNIT:	1648
EXAMINER:	HURT, Sharon L.

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR § 1.97(d)

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450
Sir:

Submitted herewith on a PTO/SB/08A form is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR § 1.56. A copy of each listed document is being submitted to comply with the provisions of 37 CFR §§ 1.97(d).

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR § 1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is

determined to be a *prima facie* prior art reference against the claims of the present application.

The Applicants also submit that no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned person after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR § 1.56(c) more than three months prior to the filing of the information disclosure statement.

STATEMENT OF RELEVANCY

WO 02/068582

The teaching of the inventors in the WO 02/068582 publication relates to the development of more stable and nuclease-resistant sequence dependent (or sequence complementary) antisense oligonucleotides that also have a higher affinity to mRNA. As a result, the inventors designed oligonucleotides containing six-membered azasugars (see page 10, lines 17-24 in WO 02/068582). As cited in Table 1 of WO 02/068582, random oligonucleotides containing six-membered azasugars (SEQ ID NOs: 20-24) are disclosed which have strong anti-HIV activity although they had no sequence specificity to *HIV-1* gene (see page 46, lines 7-10). Consequently, it is disclosed that the inhibitory effect of oligonucleotides containing six-membered azasugars on HIV-1 replication was not mediated by a sequence specific antisense mechanism against *HIV-1* gene, but rather mediated by inhibiting virus attachment on the cell surface (see page 67, lines 22-26). However, one skilled in the art would have construed from this that the antiviral activity seen was due to the six-membered azasugars, the inventors taking such an extensive departure from standard oligonucleotides. Furthermore, regarding the efficacy of the oligonucleotides disclosed in this publication, it is mentioned that these oligonucleotides did not inhibit SIV replication (page 71, lines 1-9) and poliovirus replication (page 72, lines 3-5). Thus, the oligonucleotides taught in the WO 02/068582 reference had no influence on the replication of any other viruses but HIV-1 (as mentioned on page 72, lines 23-25). Thus, this document

does not anticipate the claims as presently pending and further is a direct teaching against the present invention as now claimed.

To the contrary, the Applicants wish to first point out that the claims now in the present application are directed to 12 families of viruses not including retroviruses. Secondly, the chemical structure of the oligonucleotides described in WO 02/068582 is very different than oligonucleotides containing at least one phosphorothioate linkage as taught and claimed in the present application. Structurally speaking, WO 02/068582 publication is teaching oligonucleotides having six-membered azasugars instead of 5-membered ribose, as shown in the figure presented herein below.

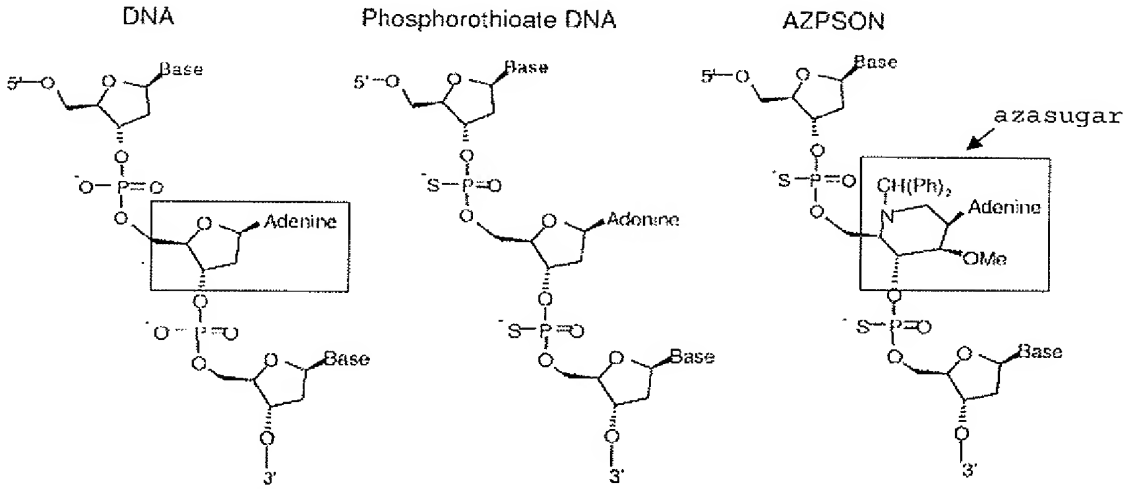


FIG. 1. Chemical structure of AZPSONs and other ONs.

(Lee *et al.*, Antimicrobial Agents and Chemotherapy, 2005, 49: 4110-4115).

Clearly, the distinction between six-membered azasugars and 5-membered ribose is important, as underlined in Fig. 1, despite the fact that visually, the 2 phenyl moieties are not fully illustrated, showing the bulkyness and steric hindrance of the molecule. The inventors in the WO 02/068582 publication went a long way to design 6-azasugars oligonucleotides. They never considered using non-six membered azasugar or phosphorothioated sequence independent oligonucleotides. Thus, one skilled in the art could conclude from the

description found in the WO 02/068582 publication that the antiviral activity of oligonucleotides containing six-membered azasugars is due to the presence of six-membered azasugars. However, SEQ ID NOs: 4 and 13 of the WO 02/068582 publication, which are straight PS-ON, have antiviral activity but these oligonucleotides are sequence complementary to HIV sequences, thus one skilled in the art would deduce from these results that the activity was either due to an antisense mechanism or to a silencing mechanism dependent on the complementarity of the sequences. One cannot conclude that this publication teaches or even suggests a sequence independent mode of action for oligonucleotides having at least one phosphorothioate modification as now claimed. Interestingly enough, as previously mentioned, the oligonucleotides disclosed in the WO 02/068582 publication had no influence on the replication of other viruses than HIV-1. To the contrary, the present application teaches and claims a method for treating viral infection caused by 12 different families of viruses, more specifically herpesviridae, poxviridae, hepadnaviridae, arenaviridae, bunyaviridae, coronaviridae, filoviridae, flaviridae, orthomyxoviridae, paramyxoviridae, rhabdoviridae and togaviridae, by administering oligonucleotides comprising at least one phosphorothioate linkage and having an antiviral activity occurring principally by a sequence independent mode of action.

In view of the facts presented hereinabove, the Applicants believe that the International application publication No WO 02/068582, taken alone or in combination with any other documents, does not anticipate or render obvious the claims of the present application.

WO 03/097661

Regarding the WO 03/097661 publication, the Applicants wish to submit that by the nature of the sequences disclosed in this publication, it was concluded that the anti-HIV activity of phosphorothioate oligonucleotides of 37-mer or longer is sequence and structure independent (see page 20, lines 22-24 of WO 03/097661 publication). It is also important to note that all examples disclosed in this publication present *in vitro* results.

In this regard, the Applicants firstly point out that the claims, as currently pending in the present application, are directed to 12 families of viruses not including retroviruses. There is no indication or even a suggestion in the WO 03/097661 reference that the disclosed oligonucleotides can inhibit infection of any other viruses, other than HIV. Furthermore, in light of the teaching of the prior art, one skilled in the art would have never thought that the effect noted in HIV-1 would have also been effective on other viruses.

Moreover, if one follows the strict guidelines from the USPTO regarding invention related to treating cancer and HIV infection, the teaching found in the WO 03/097661 publication is not enabling for a treatment against HIV infection in a subject. The specification, while being enabling for inhibition of part of the HIV life cycle *in vitro* (in cell culture), does not reasonably provide enablement for the prophylaxis or treatment of a HIV infection *in vivo*, especially if the subject is a human. It is further believed that the USPTO position is that, given the divergence of *in vitro* and *in vivo* HIV specific responses, the clinical relevance in the art would be burdened with an undue quantity of *in vivo* experiments in order to make and use the invention taught in the publication such as the WO 03/097661 reference, since it did not disclose any clear-cut evidence to demonstrate that the claimed oligonucleotides can prevent or treat HIV infection. Because of the absent working examples and specific teachings of the clinical efficacy, therapeutic index, and pharmacokinetic properties of the oligonucleotides, those with ordinary skill in the art would not be able to use the claimed method for the prophylaxis or treatment of HIV infection with the oligonucleotides claimed in the WO 03/097661 publication.

In view of the facts presented hereinabove, the Applicants believe that the International application publication No. WO 03/097661, taken alone or in combination, does not anticipate or render obvious the claims presently pending in the present application.

Further, the Applicants wish to also submit that a person skilled in the art would not be motivated and would not have any reason to combine the teaching found in the WO 03/097661 and WO 02/068582 publications. It is thus believed that there is no incentive in the WO 02/06858 publication alone or in combination with the teaching found in the WO

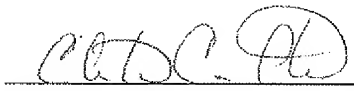
03/097661 publication, for a person skilled in the art to obtain the present invention, since none of these documents teach nor suggest a method for the prophylaxis or treatment of a viral infection in a subject as now claimed. In fact, the WO 02/068582 publication teaches in the opposite direction from the present invention, and the WO 03/097661 publication does not enable one ordinarily skilled in the art to believe that the results could be transposable to any virus or that it could indeed have antiviral in vivo.

Applicants respectfully request that any listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08A/B be returned in accordance with MPEP § 609.

The Commissioner is hereby authorized to withdraw the fees in the amount of $180.00 for the submission of an Information Disclosure Statement from Deposit Account No. 19-5113 as well as any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-5113.

Respectfully submitted,

May 14, 2007



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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/661,403
Filing Date	September 12, 2003
First Named Inventor	Andrew Vaillant et al.
Art Unit	1648
Examiner Name	Sharon L. Hurt
Attorney Docket Number	16051-4US CC

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number – Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code3 – Number4 – Kind Code5 *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant Of Cited Document	Pages, Columns, Lines Where Relevant Passages or Relevant Figures Appear	T[6]
		WO 02/068582				
		WO 03/097661				

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.**

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